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## Motexafin Lutetium Phototherapy Decreases Vascular Inflammation in Rabbit Atheroma: Implications for Vulnerable Plaque Therapy

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**Background**: Macrophage (Mac) burden is a critical determinant of plaque instability. Motexafin lutetium (MLu), an expanded porphyrin, decreases Macs in rabbit atheroma when locally administered and photoactivated. We studied the effect of MLu phototherapy on human Macs *in vitro* and the effect of systemic MLu followed by local photoactivation (732nm) on vascular Mac burden, as well as thermal effects of balloon illumination *in vivo*. **Methods**: *In vitro* Human monocytes (THP-1) were cultured with MLu (10 μg/ml), then photoactivated (2 J/cm$^2$); drug uptake (histofluorescence), growth and differentiation (cell count) were assessed. *In vivo*: After 14 wks on 2% chol, 48 rabbits were randomized to 7 groups: (1) Control (5% mannitol); (2) MLu (10 mg/kg); (3) Light (100 J/cm$^f$ in balloon, 300 J/cm$^f$ with bare fiber); and MLu + light, 10, 30, 100 and 300 J/cm$^f$ as groups 4-7. Light was delivered to upper thoracic aorta via a balloon and lower thoracic/abdominal aorta by a bare fiber for 900 secs/site, 24h after i.v. MLu. After 3 more wks, aortas were examined for plaque (I/M ratios) and Macs (RAM-11 stain). Six more animals underwent balloon illumination (30-300 J/cm$^f$) with adventitial temperatures of vessels continuously recorded by an infrared camera. **Results** *In vitro*, MLu was taken up by Macs 30 min post incubation and retained over 24h. MLu reduced monocyte differentiation to Macs (43.6% of control, p<0.01). MLu phototherapy (24h) induced apoptotic death in Macs (44.8±3.2% vs. control 9.8±1.0%, p<0.01). *In vivo*, MLu phototherapy at lower light levels reduced vascular Mac burden (% total intima area) from 28.1±4.1 (control) to 14.2±6.4 at 10 J/cm$^f$ and 16.4±5.2 at 30 J/cm$^f$ in balloon (p<0.05), and from 8.9±1.8 (control) to 4.4±1.5 at 30 J/cm$^f$ and 4.5±2.0 at 100 J/cm$^f$ with bare fiber (p<0.05), but did not change plaque burden. Adventitial temperature increased up to 15°C at 300 J/cm$^f$ and 3°C at 100 J/cm$^f$, with no change at 30 J/cm$^f$. **Conclusions**: MLu phototherapy decreases Mac burden at lower light fluence, in the absence of regression, possibly by reduction of monocyte differentiation and induction of Mac apoptosis. Thermal effects at high light fluence may reduce efficacy. MLu phototherapy may be useful in plaque stabilization.

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## Long-Term Effects of Octreotide Therapy: A Somatostatin Analog, on In-Stent Restenosis

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Background: Although somatostatin analogs have been shown to reduce neointimal reaction in animal models but to have no definitely good result in human after balloon angioplasty, their roles in reducing in-stent restenosis in human have not been evaluated. Neointimal hyperplasia shown to be decreased by the octreotide therapy is accepted as the predominate mechanism of in-stent restenosis as well as neointimal hyperplasia is only one of the major responsible mechanisms of restenosis after angioplasty. The purpose of this study was to assess the long-term effects of octreotide on the in-stent restenosis at six-month follow-up coronary angiography.

Methods: In a placebo-controlled, randomized study, of the 176 patients, the finally evaluable 148 patients with significant coronary disease (stenosis > 70%) amenable to stenting were randomly allocated to octreotide therapy with a dose of 300 mg or placebo subcutaneously every eight hours for three weeks. The primary endpoint of the study was the restenosis rate after stenting at 6-month follow-up. Restenosis was defined as recurrent lumen diameter stenosis >50% at follow-up angiography. Stenting was considered successful if the residual diameter stenosis was less than 10%.

Results: There was no significant difference between octreotide and placebo groups in the pre (85.8% ± %6.5 and 85% ± %9.4, p>0.05) and poststenting mean percent diameter stenoses (7.6% ± 2.1% vs. 7.4% ± 2.2%, p>0.05) respectively. The mean percent diameter stenoses at the 6-month control angiographies of octreotide and placebo groups were significantly different from each other. (35% ± 19.2% vs. 18.8% ± 14.2 respectively, p=0.001). At the six-month, the restenosis rate was 12% (9 of 76 patients) in the octreotide group and 26% (19 of 72 patients) in the control group. The difference between the two groups was significant (p<0.05). We found an OR of 0.37 with a 95% CI of 0.14-0.96 (p=0.036), when octreotide was given to our patients undergoing to stenting.

Conclusion: Due to our findings, octreotide caused a significant reduction on in-stent restenosis. We proposed that these results could be related to the inhibiting effect of octreotide on neointimal hyperplasia after stenting.

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## Intracoronary Calcium Channel-Blocker Is Associated With Earlier Release of Cardiac Enzymes After Coronary Intervention

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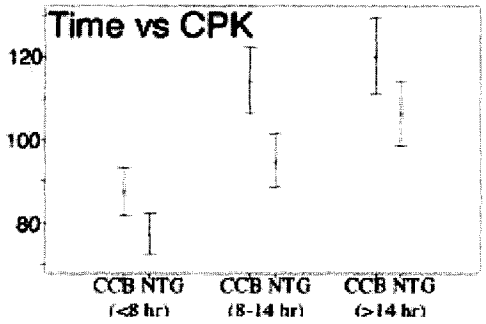
Background: Nitroglycercin (NTG) and calcium channel blockers (CCB) dilate the epicardial coronary arteries while CCB may further vasodilate the microcirculation. If microcirculation impairment plays a role in peri-procedural myocardial infarctions, we hypothesized that the use of an intracoronary (IC) calcium channel blocker during PCI would result in alterations in myocardial enzyme release after PCI compared with NTG.

Methods: 816 sequential patients, undergoing PCI without evolving infarction, were abstracted retrospectively for demographics, peri-procedural medications and details that might impact on outcome of CPK release. CPK enzymes were routinely ordered at 6, 12, and 18 hours after PCI. IC-CCB or NTG use was specifically noted and reflected operators standard choice. Post-procedural CPK levels were analyzed using both a repeated measures (ANOVA) and a random coefficient model using a quadratic function.

Results: CCB (n=401) and the NTG (n=415) had similar background characteristics and net elevations of CPK. IC-CCB group had an earlier rise in CPK (p=.0002 by 8 hrs) and an earlier peak (16.3 hrs vs 26.1 hrs) compared with the IC-NTG group.

Conclusions: Routine IC-CCB use is associated with an earlier rise of CPK enzymes after PCI. This supports the role of CCB as vasodilators of the microcirculation and suggests further avenues for research in enhancing blood flow at the tissue level of the myocardium during PCI.

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## Effect of Simvastatin on the Inflammatory Response to Coronary Angioplasty

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**Background:** Previous studies have reported treatment with the HMG-CoA reductase inhibitor simvastatin reduces serum C-reactive protein (CRP) levels, suggesting an anti-inflammatory effect that appears to be fully established within 4 weeks of commencing therapy. Coronary angioplasty is associated with an acute increase in serum inflammatory markers which may predict early complications. The effect of simvastatin on this inflammatory marker rise is unknown. The aim of this study was to determine whether pre-treatment with simvastatin reduces the inflammatory response to coronary angioplasty.

**Methods:** We studied 92 patients (mean age 60±10 years) randomised to simvastatin 40mg/d (n=52) or placebo (n=40) a median of 1.9 months (IQR 0.9 to 3.6 months) before elective coronary angioplasty. All patients were taking aspirin 150mg/day unless there was a specific contraindication (aspirin use 92% for simvastatin group, 95% for placebo group, p=ns). CRP was measured by high sensitivity immunoassay on serum samples taken immediately prior to and 48 hours after angioplasty.

**Results:** The CRP (median[IQR]) immediately prior to angioplasty was 1.3mg/l (0.71-2.43) for the placebo group, versus 1.46mg/l (0.67-2.14) for the simvastatin group, p=0.79. CRP increased post-PCI for both groups (p<0.001 for both simvastatin and placebo). Simvastatin did not alter this inflammatory response; the increase in CRP (pre-angioplasty to 48 hours post-angioplasty) for patients randomised to simvastatin was 4.68mg/l (IQR 2.9 to 10.3) compared to 5.18mg/l (IQR 2.2-9.3) for placebo, (p=0.96). Exclusion of patients on simvastatin for less than 4 weeks prior to angioplasty did not alter this result.

**Conclusion:** There is an increase in CRP measured 48 hours after angioplasty, confirming an inflammatory response. Simvastatin did not significantly influence this inflammatory response.

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## Neither Periprocedural Pregnancy-Associated Plasma Protein A nor C-Reactive Protein Levels Predict Restenosis

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**Background:** Matrix metalloproteinases including Pregnancy-Associated Plasma Protein A (PAPP-A) are abundantly expressed at sites of atherosclerotic plaque rupture, are predictive of acute coronary syndromes when circulating levels are elevated, and may play an important role in the development of restenosis following percutaneous coronary intervention (PCI). C-reactive protein (CRP) levels increase following PCI, peaking at 48 to 72 hours, but the effect of this inflammatory response on restenosis is unclear. The aim of this study was to determine whether peri-procedural levels of PAPP-A and/or CRP predict restenosis.

**Methods:** We studied 136 patients with stable angina who underwent elective PCI with stored peri-procedural blood samples and corresponding pre-, post-, and six month coronary angiograms; age (mean±SD) 59±10 yrs, 83% male, stent insertion rate 14%. CRP and PAPP-A were measured by high sensitivity immunoassay on EDTA-plasma samples which had been taken immediately prior to, and 48 hours post, PCI. All results are expressed as median (IQR). Restenosis (diameter stenosis >50%) six months after PCI was determined by quantitative coronary angiographic (QCA) analysis. In multi vessel PCI (39% of patients), analysis was done on a "per patient" basis by averaging the percent diameter stenosis of all lesions.

**Results:** PCI was associated with a significant rise in both CRP and PAPP-A levels; CRP prior to PCI 1.2mg/l (0.7-2.2), post-PCI 6.6mg/l (4.0-13.2), p<0.0001, PAPP-A prior to PCI 4.1mIU/l (3.3-5.1), post-PCI 5.8mIU/l (4.3-7.2), p<0.0001. The median stenosis at six months was 46% (IQR 34-63%) and the binary restenosis rate was 42%. There were